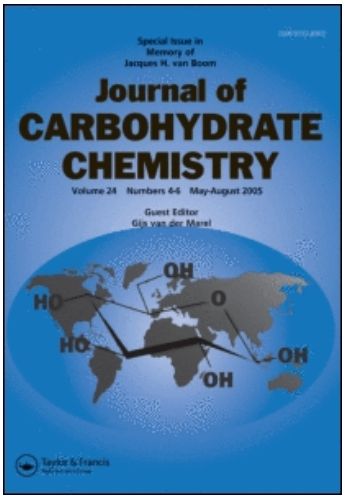

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d-Glucaric Acid Esters/Lactones Used in Condensation Polymerization to Produce Hydroxylated Nylons—A Qualitative Equilibrium Study in Acidic and Basic Alcohol Solutions

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D-GLUCARIC ACID ESTERS/LACTONES USED IN CONDENSATION POLYMERIZATION TO PRODUCE HYDROXYLATED NYLONS - A QUALITATIVE EQUILIBRIUM STUDY IN ACIDIC AND BASIC ALCOHOL SOLUTIONS

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ABSTRACT

Direct esterification of D-glucaric acid in acidic methanol solution produced a mixture of four esters/lactones: dimethyl D-glucarate (**1**), methyl D-glucarate 1,4-lactone (**2**), methyl D-glucarate 6,3-lactone (**3**), and D-glucaro-1,4:6,3-dilactone (**4**). The esters/lactones described in this study are activated forms of D-glucaric acid useful for condensation polymerization with diamines to produce hydroxyated nylons. Structures of the esterification products were determined using ^{1}H NMR, ^{13}C NMR and GC/MS techniques. Qualitative changes in equilibrium concentrations of the esters/lactones mixtures, as determined from ^{1}H NMR spectral studies, were observed in acidic (methanol-d_4/HCl) and basic (methanol-d_4/triethylamine) alcohol solutions. Esterification of D-glucaric acid in ethanol produced ethyl esters/lactones mixtures which were observed to undergo changes in equilibrium composition in acidic and basic ethanol solutions comparable to those found with the methyl esters/lactones mixtures.

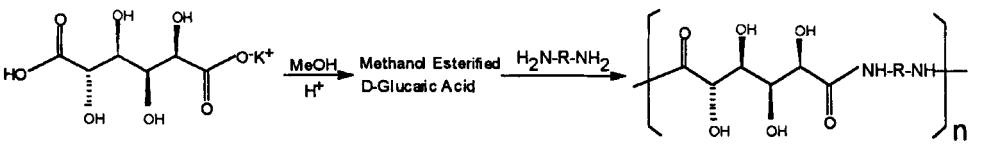
INTRODUCTION

The synthesis of hydroxylated nylons, also referred to as polyhydroxypolyamides or poly(alkylenealdaramides), by polycondensation between aliphatic primary diamines and aldaric acid diesters was first described by Ogata and coworkers in the 1970's.[1-4] These workers established that diesters of L-tartaric acid and galactaric acid (dimethyl L-tartarate[1,2] and diethyl galactarate,[3,4] respectively) underwent condensation polymerization

in polar solvents to produce insoluble hydrophilic polyamides. Condensation of these and other esters led Ogata and coworkers to conclude that, in general, diesters having heteroatoms such as oxygen or sulfur on the carbons α to the ester carbonyls are active esters, accounting for their enhanced reactivity with amines compared to that of their aliphatic counterparts.

Hoagland clarified the role that hydroxyl groups on diethyl galactarate[5] and diethyl xylarate[6] play in rapid aminolysis reactions of six and five carbon aldaric acid diesters. In the diaminolysis of either of these diesters, a fast 1,4-lactonization step precedes the slower aminolysis step, implying that acyclic dialkyl aldarates, aldarate ester/lactones or aldarate dilactones can similarly undergo diaminolysis or polymerization.

Previous work from this laboratory described the preparation of polyhydroxy-polyamides from esterified xylaric, galactaric and D-glucaric acid.[7-11] The use of D-glucaric acid as the acid monomer precursor for the preparation of hydroxylated nylons (**Scheme 1**) with potentially good biodegradability properties is of particular interest to us given the commercial availability and low cost of D-glucose as the starting material for D-glucaric acid.[10,11]



Scheme 1. Preparation of Hydroxylated Nylons from Monopotassium D-Glucarate.

Unlike the acyclic diester forms of tartaric and galactaric acids, the common esterified forms of D-glucaric acid have ester/lactone structures. In order to better understand polyhydroxypolyamide formation of esterified D-glucaric acid with diamines, we first undertook a study to determine the structures of the esters/lactone products formed from acid catalyzed methanol esterification of D-glucaric acid. A second objective of this study was to compare relative compositions of these esters/lactones mixtures in basic alcohol solutions (model conditions for polymerization with diamines) and in strongly acidic alcohol solutions.

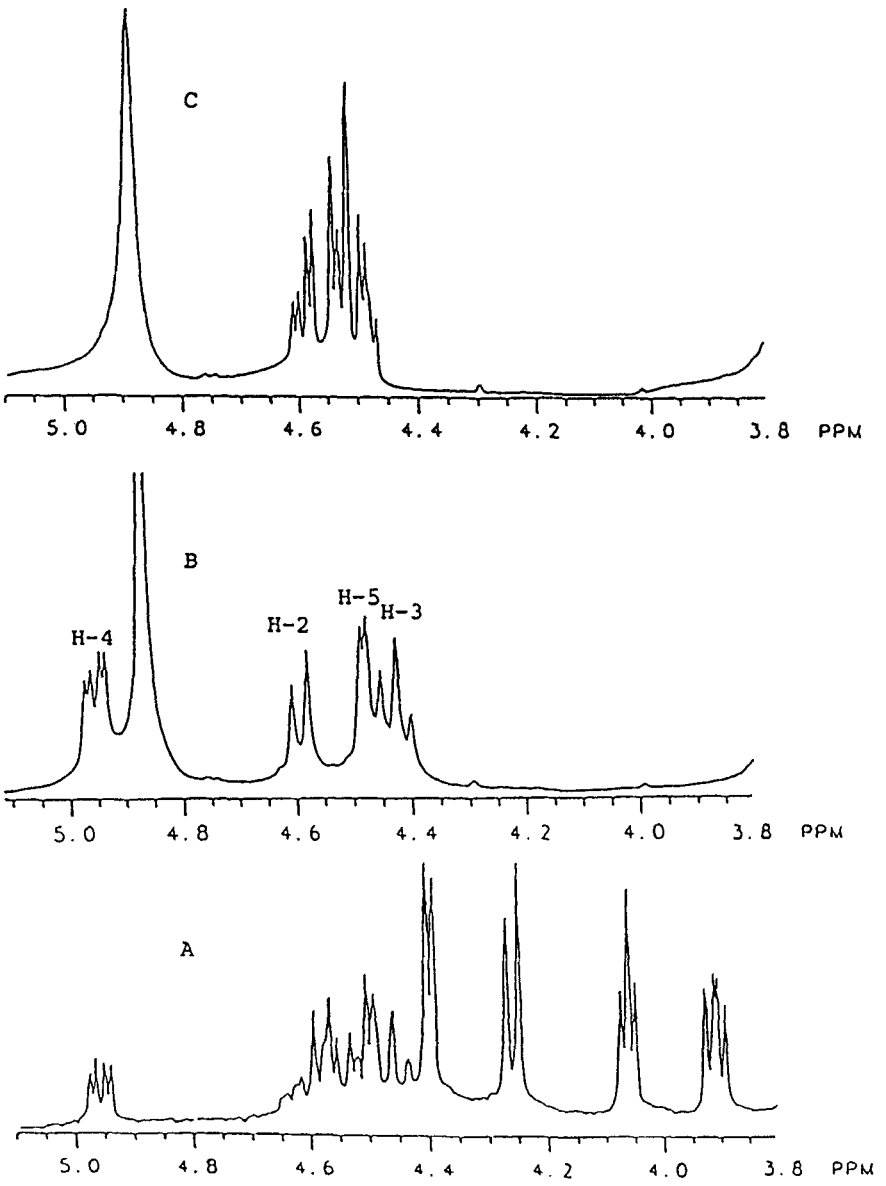


Figure 1. ^{1}H NMR Spectra (methanol-d_4) of A) Methanol Esterified D-Glucaric Acid; B) Methyl D-Glucarate 1,4-Lactone (2); C) Methyl D-Glucarate 6,3-Lactone (3).

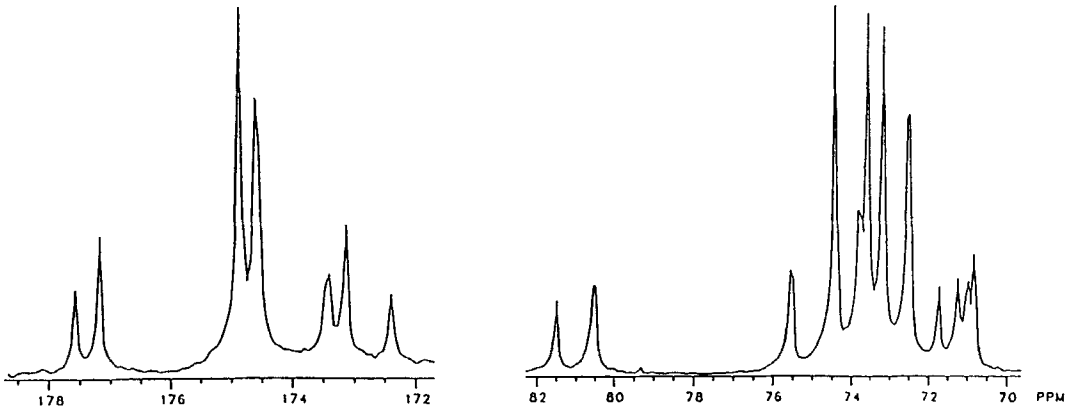


Figure 2. ^{13}C NMR Spectrum (methanol-d_4) of Methanol Esterified D-Glucaric Acid from Treating Monopotassium D-Glucarate with Methanol/Acetyl Chloride.

RESULTS AND DISCUSSION

Methanol Esterified D-Glucaric Acid - Preparation and General ^1H and ^{13}C NMR Characteristics. For purposes of this study, methanol esterified D-glucaric acid was prepared by warming a mixture of solid, insoluble monopotasssium D-glucarate with methanolic HCl (acetyl chloride in methanol). Following removal of insoluble KCl by filtration, concentration of the filtrate yielded a syrupy esterification product. A sample of this product was dissolved in methanol-d_4 and its ^1H NMR spectrum recorded (**Fig. 1**). The C-H_2 to C-H_5 glucaro protons of the products are found between δ 3.85 and 5.0 ppm. Small multiplets between δ 3.60 to 3.75 ppm result from residual methyl ester groups that survived transesterification during dissolution of the methanol esterification product in methanol-d_4. Large broad methyl proton signals at ~ δ 3.35 ppm are from methanol, liberated during transesterification, and residual methyl acetate carried over in the syrupy product. A DOH signal (δ 5.45 ppm) was well separated from the glucaro C-H protons.

The ^{13}C NMR spectrum of the product (**Fig. 2**) contains six carbohydrate carbonyl carbon signals (a seventh carbonyl signal at 173.42 arises from methyl acetate) and twelve carbohydrate non-carbonyl signals (70-82 ppm). The methyl ester carbon signals appear unresolved in the 48-55 ppm region of the spectrum. Consequently, it is clear from this spectrum that methanol esterified D-glucaric acid contains three distinct structural forms.[10,11]

GC/MS Analysis of A Methanol Esterified D-Glucaric Acid Mixture. It was reported by Hirasaka and coworkers[12] and by Horton and Walaszek[13] that an aqueous solution of D-glucaric acid contains three components in equilibrium; acyclic D-glucaric acid, D-glucaro-1,4-lactone and D-glucaro-6,3-lactone. These results suggested that the three methanol esterified forms of D-glucaric acid are the ester forms of the same three acid structures. To test this idea, a sample of methyl D-glucaro-1,4-lactone (**2**)[10,13] was trimethylsilylated[14] and a sample (in chloroform) subjected to GC/MS analysis. The major total ion chromatogram peak from this sample (~ 90 %, retention time 2.07 min) had a molecular ion at m/z 422 corresponding to the fully trimethylsilylated lactone/ester. Methanol esterified D-glucaric acid was similarly trimethylsilylated and subjected to GC/MS analysis under the same conditions to give a three component mixture (total ion chromatogram, **Fig. 3**). Of the three components, the one of retention time 8.15 min has its highest mass/charge peak at 422 and corresponds to trimethylsilylated methyl D-glucarate 1,4-lactone. A second trimethylsilylated methyl D-glucarate lactone of retention time 8.45 min was also identified with a mass/charge peak at 422. The third trimethylsilylated component at retention 8.28 min has an M^+ peak at m/z 511 but no 422 peak, consistent with the dimethyl 2,3,4,5-*tetrakis*-*O*-(trimethylsilyl)-D-glucarate structure.

Assignment of Structures in Methanol Esterified D-Glucaric Acid. The GC/MS results as described implied that the three component methanol esterified mixture was composed of dimethyl D-glucarate (**1**) and two methyl D-glucarate lactones, one of which was methyl D-glucarate 1,4-lactone (**2**) and the other being most likely methyl D-glucarate 6,3-lactone (**3**). The methyl esters of D-glucarate 1,4-lactone (**2**) and 6,3-lactone (**3**) were prepared according to the procedure of Reeves,[16] by treating D-glucaro-1,4-lactone and D-glucaro-6,3-lactone, respectively, with diazomethane. The ^{1}H NMR spectra of the ester/lactones **2** and **3** were compared with the spectrum of the mixture (**Fig. 1**). In the spectrum of methyl D-glucarate 1,4-lactone (**2**), one of the four proton signals is well separated from the other three as a doublet of doublets (4.97 ppm). In keeping with general trends used to assign carbohydrate δ - lactones,[13] this signal is assigned to H-4 which is bonded to the carbon connected to the lactone ring oxygen. The remaining assignments are H-2 at 4.60 ppm, H-3 at 4.44 ppm and H-5 at 4.49 ppm. The proton chemical shifts from methyl D-glucarate 6,3-lactone (**3**) are in a somewhat narrow range, but as with the 1,4-lactone, the proton on the carbon connected to the ring oxygen (H-3)

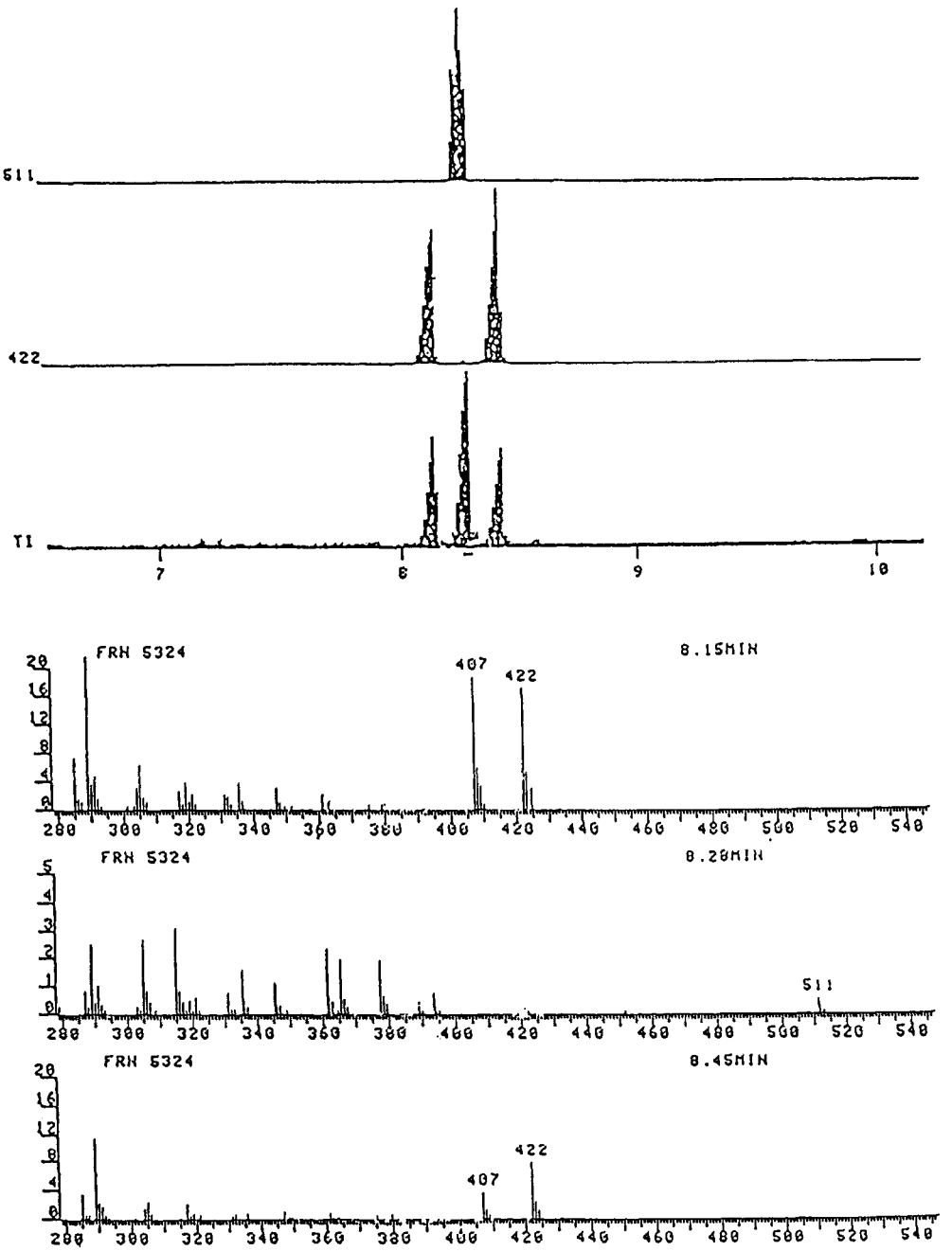


Figure 3. Total Ion and Selective Ion GC Chromatograms (top) and Mass Spectra (bottom) from a Trimethylsilylated Methanol-Esterified D-Glucaric Acid Mixture.

Table 1. ^{13}C NMR Chemical Shifts (methanol-d_4) from Methanol Esterified D-Glucaric Acid Mixture Compared to Those from Methyl D-Glucarate 1,4-Lactone and Methyl D-Glucarate 6,3-Lactone

Mixture (δ)	177.58	177.19	174.87	174.59	173.42a	173.15	172.38	81.50	80.50
1,4-Lactone (**2**)		177.35				173.19			80.49
6,3-Lactone (**3**)	177.55						172.29	81.66	

Mixture (δ)	75.52	74.40	73.76	73.54	73.14	72.48	71.72	71.23	70.97	70.82
1,4-Lactone (**2**)	75.54		73.68							70.79
6,3-Lactone (**3**)							71.77	71.11	71.03	

a. The peak at 173.42 ppm is from the carbonyl carbon of methyl acetate.

Table 2. ^{13}C NMR Chemical Shifts (Methanol-d_4) of Methyl D-Glucarate Lactones

Carbon Number	1	2	3	4	5	6
6,3-Lactone (**3**)	172.29	71.11	81.66	71.03	71.77	177.55
1,4-Lactone (**2**)	177.35	75.54	70.79	80.49	73.68	173.19

is assigned to the most downfield signal (4.60 ppm). The H-2 and H-5 signals overlap at 4.54 ppm and H-4 (dd) is at 4.49 ppm.

Identification of methyl ester/lactones **2** and **3** as components of the esterification mixture was further supported from matching the ^{13}C NMR signals of authentic **2** and **3** with these in the mixture (Table 1). Comparison of the ^{13}C NMR data from authentic **2** and **3** is presented in Table 2. The lactone carbonyl carbon in both compounds is the most deshielded[10] followed by the exocyclic ester carbonyl carbon and then the carbon attached to the ring oxygen (C-4 for 1,4-lactone **2** and C-3 for 6,3-lactone **3**). As presented in the previous section, GC/MS data from the trimethylsilylated mixture implied that the third component in the mixture was dimethyl D-glucarate. In keeping with this structure, the four upfield signals in the ^{1}H NMR spectrum of the mixture (**Fig. 4A**) are assigned to dimethyl D-glucarate (**1**) H-2 - H-5 (**Table 3**). Authentic dimethyl D-glucarate

Table 3. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants (Hz); Dimethyl D-Glucarate in Methanol Esterified D-Glucaric Acid Mixture and Dimethyl D-Glucaramide

Proton Number	H-2	$J_{2,3}$	H-3	$J_{3,4}$	H-4	$J_{4,5}$	H-5
Dimethyl Ester (CD_3OD)	4.38 (d)	3.63	4.05 (dd)	4.74	3.90 (dd)	6.43	4.25 (d)
Glucaramide (D_2O)	4.32 (d)	2.79	4.10 (dd)	4.82	3.97 (dd)	5.05	4.25 (d)

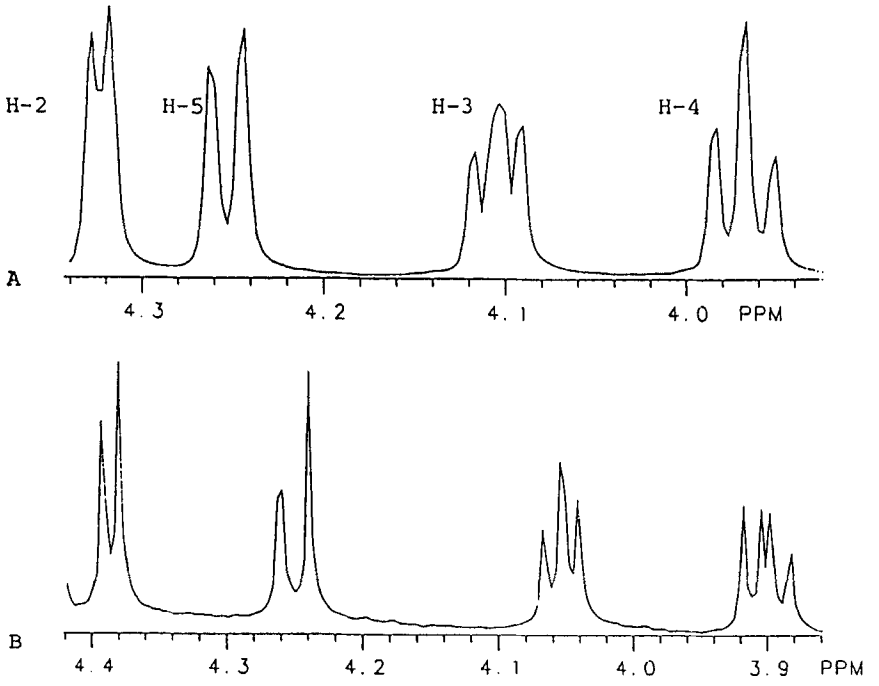
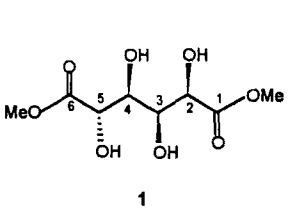


Figure 4. ^{1}H NMR Spectra of H-2 to H-5 in: A) Methanol Esterified D-Glucaric Acid (methanol-d_4) - Upfield Region (see Fig. 1); B) Dimethyl D-Glucaramide (D_2O).

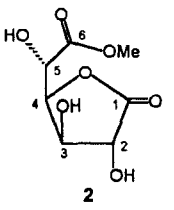
was not available for comparison but *N,N'*-dimethyl-D-glucaramide was a reasonable ^{1}H NMR model (**Fig. 4B**) for the diester (**Table 3**). ^{1}H NMR chemical shift assignments for both the glucaramide and dimethyl ester protons are based upon decoupling experiments. The largest vicinal coupling is between H-4 and H-5, in keeping with the relatively large dihedral angle between these protons in the conformationally extended part of the molecule.[17]

Results from GC/MS, ^{13}C NMR and ^{1}H NMR analyses of the methanol esterified D-glucaric acid mixture all indicate a three component system composed of dimethyl D-glucarate (**1**), methyl D-glucarate 1,4-lactone (**2**) and methyl D-glucarate 6,3-lactone (**3**).



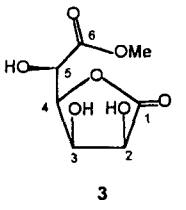
1

Dimethyl D-Glucarate



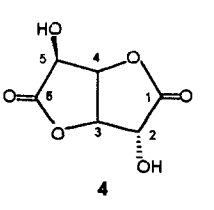
2

Methyl D-glucarate 1,4-lactone



3

Methyl D-glucarate 6,3-lactone



4

D-Glucaro-1,4;6,3-dilactone

Effect of Prolonged Drying of A Methanol Esterified D-Glucaric Acid Mixture at Reduced Pressure. In an attempt to remove remaining amounts of HCl from the methanol esterified D-glucaric acid mixture, the syrupy product was dried at reduced pressure (0.25 torr) and 70 °C for 12 hours. The ^{1}H NMR spectrum (methanol-d_4) of the mixture (**Fig. 5A**) was significantly different from those of typically less rigorously dried samples, showing very little dimethyl D-glucarate (**1**), but indicating the emergence of a new major component with signals in the downfield region of the spectrum. The downfield ^{1}H NMR chemical shift positions of the new signals suggested that the new component formed with heating under vacuum was the bicyclic derivative D-glucaro-1,4:6,3-dilactone (**4**). To verify this structural assignment, a sample of authentic dilactone[12] was prepared by melting methyl D-glucarate 1,4-lactone (**3**) under vacuum. The signals in the ^{1}H NMR spectrum of dilactone **4** (**Fig. 5B**, D_2O) corresponded to these of the new signals from the vacuum dried methanol esterified D-glucaric acid mixture (**Fig. 5A**, methanol-d_4), confirming the structural assignment.

Change in the Composition of Methanol Esterified D-Glucaric Acid In Strong Acid Alcohol Solution (Methanol/HCl) and Tertiary Amine Alcohol Solution (Methanol/Triethylamine).

In order to better understand the equilibrium relationship between these four D-glucaric acid ester/lactone forms, equilibria were established under different conditions of acid and base as described in the following sections.

Methanol/HCl Solution. The mixture from a typical vacuum dried methanol-esterified D-glucaric acid preparation (**Fig. 6A**) was dissolved in methanol-d_4 containing

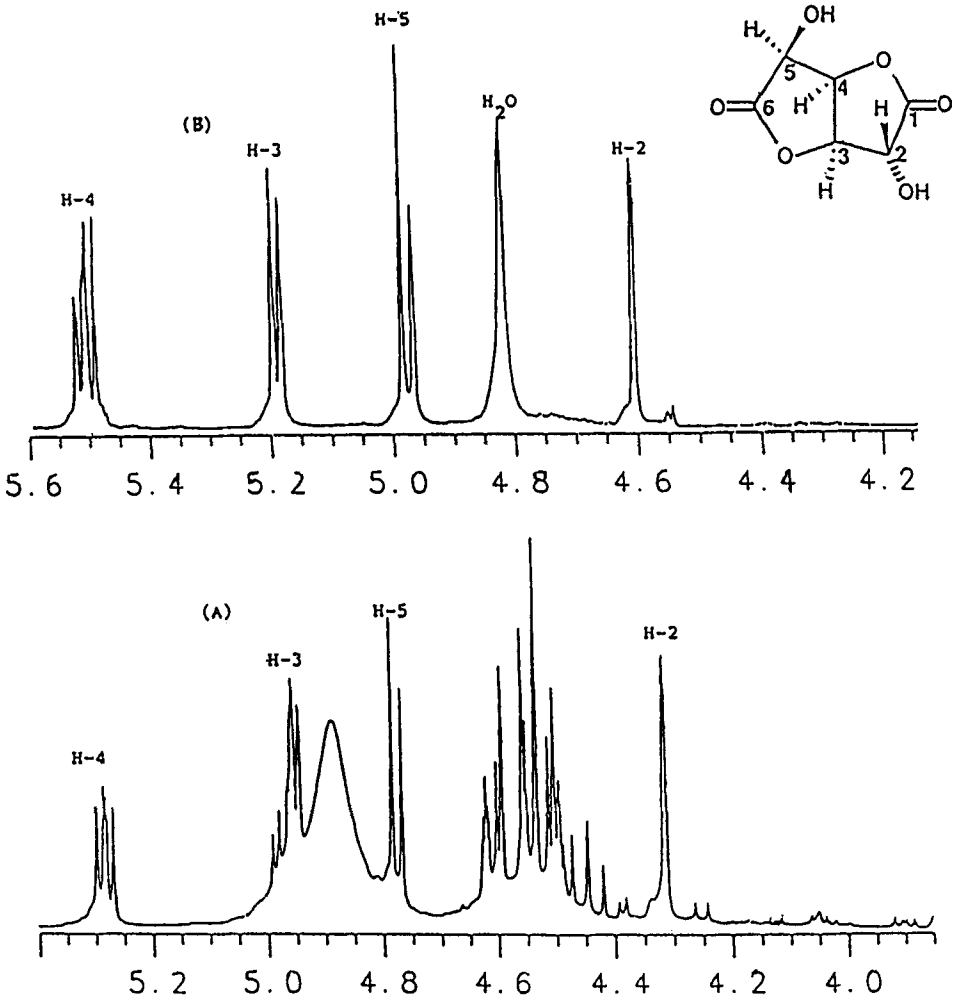


Figure 5. ^{1}H NMR Spectrum of A) Vacuum Dried and Heated Methanol Esterified D-Glucaric Acid (methanol-d_4); B) Authentic D-Glucaro-1,4;6,3-dilactone (D_2O).

HCl. Within ten minutes (**Fig. 6B**) very little D-glucaro-1,4:6,3-dilactone (**4**) remained and the mixture was principally composed of the 1,4- and 6,3-lactones, **2** and **3**, respectively. A spectrum recorded after two hours (**Fig. 6C**) showed no dilactone was present but the solution did contain a significant amount of dimethyl D-glucarate (**1**), in addition to the two five-membered lactones. After twenty hours dimethyl D-glucarate (**1**) became the principal component of the mixture (**Fig. 6D**). Comparable equilibration was also observed beginning with methyl D-glucarate 1,4-lactone.

Methanol-d_4/Triethylamine Solution. Methyl D-glucarate 1,4-lactone (**2**), a typical starting material for polymerizations with diamine, was dissolved in methanol-d_4 to which a small amount of triethylamine was added. The ^{1}H NMR spectra of the solution recorded over time showed rapid establishment of the three component mixture (no 1,4:6,3 dilactone) with dimethyl D-glucarate (**1**) as the most abundant component. These results clearly indicated that in starting with a single ester/lactone form of D-glucaric acid under typical polymerization conditions,[10,11] an equilibrium mixture of **1**, **2**, and **3** was formed.

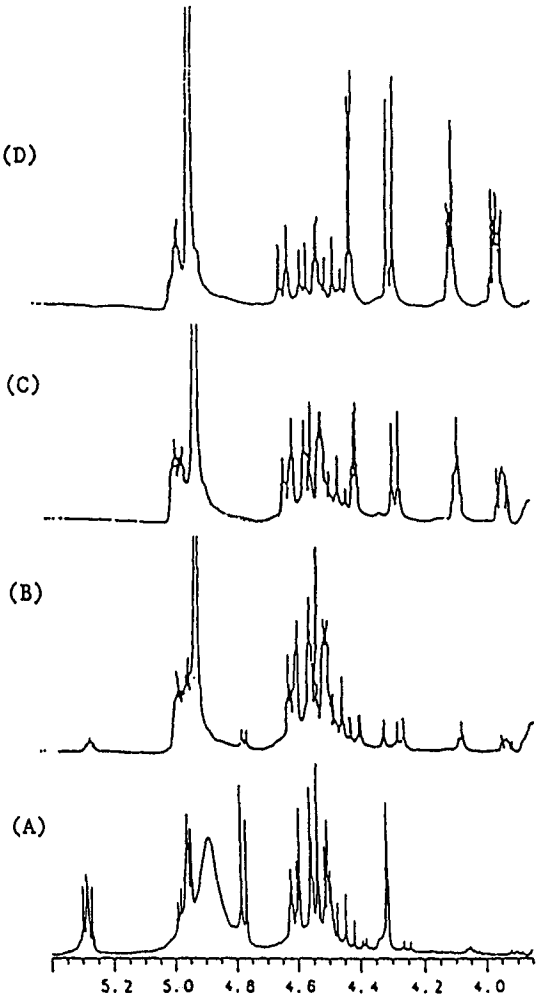


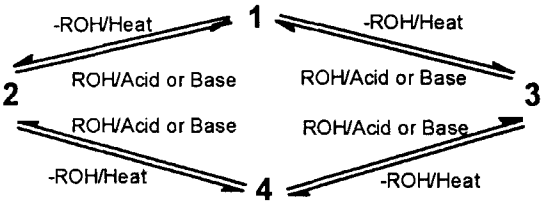
Figure 6. ^{1}H NMR (methanol-d_4) of A) Vacuum Dried and Heated Methanol Esterified D-Glucaric Acid; B) 10 min after Addition of HCl; C) 2 h after Addition of HCl; D) 20 h after Addition of HCl.

Equilibration of Ethyl D-Glucarate 6,3-Lactone in Acidic (HCl) and Basic (Triethylamine) Ethanol Solutions.

Ethyl D-glucarate 6,3-lactone[10,11] (**5**) is also a useful starting material for polymerization to produce poly(alkylene D-glucaramides). Consequently, knowing something about its equilibrium behavior in basic (and acidic) ethanol solution was of interest to us. The ^{1}H NMR spectrum of **5** in ethanol-d_6 containing acetyl chloride showed that a typical three component 1,4- and 6,3-lactone and diester mixture was formed. A mixture of the same three components was also obtained by adding triethylamine to a solution of **5** in ethanol-d_6.

SUMMARY

Scheme 2 summarizes the results of the equilibrium studies employing methanol esterified D-glucaric acid, but is applicable to other alcohol esterified D-glucaric acid mixtures as well. In basic (triethylamine) or acidic (HCl) solution, dimethyl D-glucarate (**1**) is the dominant form in equilibrium with two five membered lactones, methyl D-glucarate 1,4-lactone (**2**) and methyl D-glucarate 6,3-lactone (**3**). Extended drying of the mixture under vacuum shifts the equilibrium toward D-glucaro-1,4:6,3-dilactone (**4**).



Scheme 2. Equilibrium Reactions of D-Glucaric Acid in Acid/Base Alcohol Solutions.

EXPERIMENTAL

General methods. All ^{1}H and ^{13}C NMR were recorded using a GE 300WB FT-NMR spectrometer at 300.13 and 75.4 MHz respectively. Chemical shifts are reported as ppm (δ) downfield from tetramethylsilane. GC/MS analyses were carried out using a Hewlett-Packard 5985 System, 70 eV and the EI mode. The following GC column conditions were employed: column, Ultra 2 (Crosslinked 5% Ph Me Silicon), 15 psig/He; temp 50 - 320 °C, 30 °C/min. All solvents used were reagent grade. Solvent evaporations were carried out at reduced pressure. Melting points were recorded with a Fisher-Johns Melting Point Apparatus and are reported uncorrected.

Mixture of Dimethyl D-Glucarate (1), Methyl D-Glucarate 1,4-Lactone (2) and Methyl D-Glucarate 6,3-Lactone (3) from Methanol Esterified D-Glucaric Acid. Monopotassium D-glucarate (1.00 g, 4.03 mmol) was added to a 100 mL round-bottom flask containing methanol (15 mL). To the suspended mixture was added a solution of methanolic HCl prepared by carefully addition of acetyl chloride (1.0 mL, 13.8 mmol) to ice cold methanol (10 mL). The reaction mixture was refluxed for 3-4 h, insoluble solid potassium chloride was removed by filtration and the filtrate was concentrated to give a

thick syrup. From the ^1H NMR and ^{13}C NMR spectral data of the syrup in methanol-d_4 (Tables 1 - 3) it was concluded that the esterification product was a mixture of three components of (**1**), (**2**) and (**3**).

Trimethylsilylation of a Methanol-Esterified D-Glucaric Acid Mixture. A solution of pure methyl D-glucarate 1,4-lactone (**2**, 2.00 g, 9.70 mmol) in methanol (20 mL) and acetyl chloride (0.5 mL) was refluxed for 12 h and then concentrated to a syrup whose composition (^1H NMR in methanol-d_4) was similar to that from the methanol esterification of D-glucaric acid. The syrup was then stirred at room temperature for two days with a solution of chlorotrimethylsilane (20.0 mL, 153.5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (29 mL) and dry pyridine (50 mL). The trimethylsilylation mixture was concentrated, the light yellow residue stirred with dichloromethane (20 mL) for 3 h at room temperature and the undissolved solids removed by filtration using a sintered glass funnel. The golden yellow filtrate was concentrated and then stirred with hexane (15 mL). Undissolved solids were removed by filtration and the filtrate concentrated to give a golden yellow glass which was dissolved in chloroform for GC/MS analysis ($CHCl_3$). The mixture contained three components identified as follows: methyl 2,3,5-*tris*-*O*-[trimethylsilyl]-D-glucarate 1,4-lactone, retention time 8.15 min, m/z 422 (M^+), m/z 407 ($M^+ - CH_3$); dimethyl 2,3,4,5-*tetrakis*-*O*-[trimethylsilyl]-D-glucarate, retention time 8.45 min, m/z 511 ($M^+ - CH_3$), m/z 495 ($M^+ - CH_3 - H$); methyl 2,4,5-*tris*-*O*-[trimethylsilyl]-D-glucarate 6,3-lactone, 8.45 min, m/z 422 (M^+), m/z 407 ($M^+ - CH_3$).

Trimethylsilylation of Methyl D-Glucarate 1,4-Lactone. A solution of pure methyl D-glucarate 1,4-lactone[14] (**2**, 0.500 g, 2.43 mmol) in methanol (10 mL) was stirred at room temperature with chlorotrimethylsilane (3.8 mL, 29.2 mmol), 1,1,1,3,3,3-hexamethyldisilazane (5.8 mL) and dry pyridine (34 mL). The trimethylsilylation mixture was concentrated and the light yellow residue was stirred with dichloromethane (20 mL) for 3 h at room temperature. The undissolved solids were removed by filtration using a sintered glass funnel and the golden yellow filtrate was concentrated and then stirred with hexane (15 mL). Undissolved solids were removed by filtration and the filtrate concentrated to give a golden yellow glass which was dissolved in chloroform for GC/MS analysis ($CHCl_3$): methyl 2,3,5-*tris*-*O*-[trimethylsilyl]-D-glucarate 1,4-lactone, retention time 7.07 min, m/e 422 (M+), m/z 407 ($M^+ - CH_3$).

Methyl D-Glucarate 1,4-Lactone (2).[14] The glassware used in the following procedure involving use of diazomethane was new and checked for cracks and sharp edges to avoid possible explosion. A solution of D-glucaro-1,4-lactone (D-saccharic acid 1,4-lactone, 0.200 g, 1.04 mmol, Sigma) in acetone (20 mL) was added to a 250 mL Erlenmeyer flask cooled in an ice bath. To a 500 mL Erlenmeyer flask were added 43% aqueous potassium hydroxide solution (100 mL) and ether (100 mL). To the mixture, also cooled in an ice bath, was slowly added α-methyl-α-nitrosourea (2.8 g) with stirring until the solid dissolved. A portion of the top yellow ethereal diazomethane layer was carefully decanted into the cold lactone/acetone solution until the yellow color persisted. A few more drops of ethereal diazomethane were then added to the lactone solution, the mixture was stirred for 10 min, and glacial acetic acid was added dropwise until the yellow color disappeared. Excess diazomethane from the KOH/ethereal diazomethane mixture was decomposed by careful dropwise addition of glacial acetic acid. The methylated lactone solution was concentrated to a syrup and the crude methyl D-glucarate 1,4-lactone that crystallized within ten minutes was triturated with a few drops of ethanol. Removal of the solid by filtration followed by air drying gave methyl D-glucarate 1,4-lactone (0.150 g, 0.728 mmol, 69.8%): mp 160 °C (lit.[13] 165 °C); IR (KBr) 3400 cm^{-1}, O-H stretch), 1781 cm^{-1} (five membered ring lactone C=O), 1728 cm^{-1} (ester C=O); ^1H NMR (CD_3OD) δ 4.97 (dd, 1H, H-4, $J_{4,5}$ = 2.36 Hz), 4.60 (d, 1H, H-2, $J_{2,3}$ = 8.15 Hz), 4.49 (d, 1-H, H-5), 4.44 (dd, 1H, H-3, $J_{3,4}$ = 7.31 Hz), 3.73 (s, 3H, -C$\underline{H}_3$). A convenient large scale preparation of **2** is described in references 10 and 11.

Methyl D-Glucarate 6,3-Lactone (3). The preceding diazomethylation procedure was applied to a solution of D-glucaro-6,3-lactone (D-saccharic acid 6,3-lactone, 0.200 g, 1.04 mmol, Sigma) in acetone (20 mL). The solution of methylated lactone was concentrated to a syrup and the crude methyl D-glucarate 6,3-lactone that crystallized over 3 h was triturated with a few drops of ethanol. Removal of the solid by filtration followed by air drying gave methyl D-glucarate 6,3-lactone (**3**, 0.050 g, 0.24 mmol, 23%): ^1H NMR (CD_3OD) δ 4.59 (dd, 1H, H-3, $J_{3,4)}$ = 2.92 Hz), 4.53 (d, 1H, H-2, $J_{2,3}$ = 7.35 Hz), 4.53 (d, 1H, H-5, $J_{4,5}$ = 4.64 Hz), 4.49 (dd, 1H, H-4), 3.79 (s, 3H, C$\underline{H}_3$-O). We observed, as Reeves had reported,[15] that this ester/lactone was not very stable and could not be kept for any length of time without decomposing.

Dimethyl D-Glucaramide. To a solution of methyl D-glucarate 1,4-lactone (**2**, 1.00 g, 4.85 mmol) in methanol (20 mL) at room temperature was added methylamine (1.0 mL, 13 mmol, 40% in H_2O) with stirring. The colorless solution became light yellow immediately and a white solid precipitated from the solution within 5 min. The mixture was kept stirring for 2 h, the white crystalline product was removed by filtration, washed with methanol (3 x 5 mL) and acetone (3 x 5 mL), and dried at reduced pressure (0.25 torr) at 65 °C for 6 h to give dimethyl D-glucaramide (1.04 g, 4.41 mmol, 90.9%): mp 188-190 °C; ^{1}H NMR (D_2O) δ 4.32 (d, 1H, H-2, $J_{2,3}$ = 2.79 Hz), 4.10 (dd, 1H, H-3, $J_{3,4}$ = 4.82 Hz), 3.97 (dd, 1H, H-4, $J_{4,5}$ = 5.05 Hz), 4.25 (d, 1H, H-5), 3.80 (s, 6H, N-C$\underline{H}_3$).

Anal. Calcd for $C_8H_{16}N_2O_6$: C, 40.08; H, 6.83; N, 11.86. Found: C, 40.59; H, 6.88; N, 11.83.

Methanol Esterified D-Glucaric Acid Mixture After Prolonged Drying Under Vacuum. Methanol esterified D-glucaric acid mixture, as prepared above, was further dried under vacuum (0.25 torr) at 70 °C for 12 h. The syrupy mixture was observed to bubble during the heating process. A thick syrup was obtained and its ^{1}H NMR spectrum (methanol-d_4) indicated, in addition to two five-membered lactones, a new component, D-glucaro-1,4:6,3-lactone; δ 5.28 (dd, 1H, C-4, $J_{3,4}$ = 3.43 Hz), 4.95 (dd, 1H, C-3, $J_{2,3}$ = 0.64 Hz), 4.77 (d, 1H, H-5, $J_{4,5}$ = 5.07 Hz), 4.31 (s, 1H, H-2).

D-Glucaro-1,4:6,3-dilactone[12] (**4**). A 100 mL round-bottomed flask containing solid methyl D-glucarate 1,4-lactone (**2**, 1.00 g, 4.85 mmol) was held under vacuum (0.25 torr). The flask was immersed in an oil-bath which was gradually heated to 110 °C by which temperature the methyl D-glucarate 1,4-lactone melted with bubbling. After the bubbling ceased (about 12 h), the contents were returned to atmospheric pressure and dry acetone (5 mL) added to dissolve the glassy solid on the walls of the flask. The acetone solution was concentrated and seeded with crystalline D-glucaro-1,4:6,3-dilactone resulting in the crystallization of the syrup in 5 h. The crystalline solid was dried under vacuum to give D-glucaro-1,4:6,3-dilactone (**4**, 0.826 g, 4.75 mmol, 98.0%): mp 130 °C (lit.[11] 132 °C); IR (KBr) 3385 cm^{-1} (broad, O-H, stretch), 1790 cm^{-1} (lactone, C=O); ^{1}H NMR (D_2O) δ 5.51 (t, 1H, H-4, $J_{4,5}$ = 5.37 Hz), 5.19 (d, 1H, H-3, $J_{3,4}$ = 3.85 Hz), 4.98 (d, 1H, H-5), 4.61 (s, 1H, H-2); ^{13}C NMR (D_2O) δ 178.28 (carbonyl, C-1 and C-6), 82.81 (C-4), 81.68 (C-3), 73.65 (C-2), 71.38 (C-5). Ethyl D-glucarate 1,4-lactone was used with similar success

as the starting material for **4**, with melting and bubbling of the melt occurring at an oil bath temperature of 105 °C.

***In Situ* ^{1}H NMR Analysis of Methanol Esterified D-Glucaric Acid Mixture in Methanol-d_4/HCl Solution.** A sample of a well dried methanol esterified D-glucaric acid mixture was dissolved in methanol-d_4 and transferred to a 5 mm NMR tube. To this mixture was added a drop of acetyl chloride and the ^{1}H NMR spectra of the solution recorded at 10 min, 2 h and 20 h, respectively (**Fig. 6**).

***In Situ* ^{1}H NMR Analysis of the Mixture from Methyl D-Glucarate 1,4-Lactone** (2) **in Methanol/Triethylamine Solution.** Methyl D-glucarate 1,4-lactone (**2**, 20 mg) in a 5 mm NMR tube was dissolved in methanol-d_4 containing a drop of triethylamine and ^{1}H NMR spectra of the solution were recorded at 10 min and 4.5 h, respectively, showing the same three component mixture of **1, 2** and **3** as obtained from methanol esterified D-glucaric acid.

***In Situ* ^{1}H NMR Analysis of the Mixture from Ethyl D-Glucarate 6,3-Lactone (5) in Ethanol-d_6/Acetyl Chloride Solution.** Ethyl D-glucarate 6,3-lactone[10,11] (**5**, 20 mg) was dissolved in ethanol-d_6 solvent (1 mL) and the solution transferred to a 5 mm NMR tube. One drop of acetyl chloride was added to the solution and its ^{1}H NMR spectrum was recorded after 20 min showing a three component mixture comparable to that from methanol esterified D-glucaric acid.

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